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(21) International Application Number: PCT/US98/16015 (22) International Filing Date: 3 August 1998 (03.08.98) (30) Priority Data: 60/055,568 13 August 1997 (13.08.97) US 60/071,364 15 January 1998 (15.01.98) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventor: ATWAL, Karnail, S.; 92 Valley View Way, New- town, PA 18940 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Com- pany, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: ENANTIOMERS OF 4-[[[(CYANOIMINO)- [(1,2,2-TRIMETHYLPROPYL) AMINO]METHYL]AMINO] BENZONITRILE (57) Abstract <p>The (R)-enantiomer of 4-[[[(cyanoimino)-[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile as well as the corresponding (S)-enantiomer are useful for promoting hair growth such as in male pattern baldness.</p>		

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ENANTIOMERS OF 4-[[(CYANOIMINO) [(1,2,2-
TRIMETHYLPROPYL) AMINO] METHYL] AMINO] BENZONITRILE

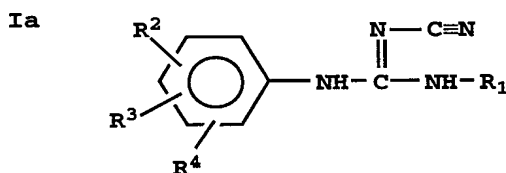
Field of the Invention

5 The present invention relates to the (R)-
and (S)-enantiomers of 4-[[(cyanoimino) [(1,2,2-
trimethyl-propyl) amino] methyl] amino] benzonitrile,
pharmaceutical compositions containing same, and a
method for promoting hair growth employing such
10 enantiomers.

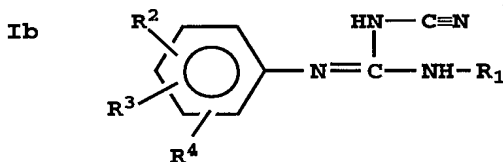
Background of the Invention

Potassium channel openers such as minoxidil
(Upjohn), pinacidil (Lilly) and diazoxide (Shiseido
15 and Schering-Plough) are known for their hair
growth stimulating activity. Thus, U.S. Patent
Nos. 4,596,812 and 4,139,619 disclose use of
minoxidil in the treatment of male pattern
baldness, alopecia areata and balding in females.
20 U.S. Patent No. 4,057,636 discloses pinacidil.
DE 3,827,467A discloses combinations of minoxidil
and hydrocortisone or retinoids.

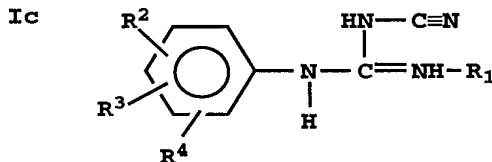
U.S. Patent No. 5,011,837 to Atwal et al
discloses aryl cyanoguanidines which possess
25 potassium channel activating activity and are
useful therapy for hypertension and other
cardiovascular disorders, for various central
nervous system disorders, kidney and urinary
problems as well as for the promotion of hair
30 growth, for example in the treatment of male
pattern baldness (alopecia). These aryl
cyanoguanidines have the structure



and its possible tautomers



and



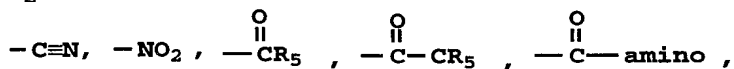
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including pharmaceutically acceptable salts,
wherein

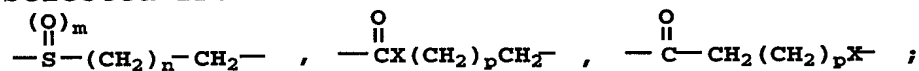
R_1 is alkyl, alkenyl, alkynyl, haloalkyl,
cycloalkyl, aryl, arylalkyl or cycloalkylalkyl;

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R_2 is



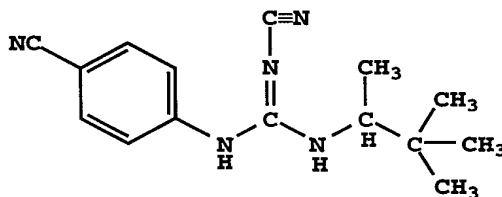
15 R_3 and R_4 are each independently selected
form $-R_2$, hydrogen, alkyl, alkenyl, alkynyl,
haloalkyl, halo, alkoxy, $-\text{NHalkyl}$, $-\text{N}-(\text{alkyl})_2$, $-\text{S}-$
alkyl, $-\text{O}-\text{aryl}-\text{alkyl}$, $-\text{S}-\text{arylalkyl}$ or $-\text{S}-\text{aryl}$, $-\text{O}-$
aryl, $-\text{NHaryl}-\text{alkyl}$, or R_2 and R_3 taken together
are a group which form a ring with the two carbon
20 atoms to which they are attached, which group is
selected from



wherein

25 $m=1$ or 2 ,
 $n=3-5$,
 $p=2-4$,
 X is 0 , NR_5 , CH_2 ; and
 R_5 is hydrogen or R_1 .

Example 1 of U.S. Patent No. 5,011,837 discloses the preparation of 4-[[[(cyanoimino)-[(1,2,2-trimethylpropyl)amino]benzonitrile



5

in the form of its racemic mixture.

PCT Application WO 92/02225 discloses a combination of a potassium channel opener and a 5- α -reductase inhibitor for promoting hair growth.

10

PCT Application WO 92/09259A discloses use of an androgen blocker and a potassium channel activator for stimulation of hair growth.

Description of the Invention

15

In accordance with the present invention, it has been unexpectedly found that the (R)-enantiomer of 4-[[[(cyanoimino)-[(1,2,2-trimethylpropyl)amino]-methyl]amino]benzonitrile, including

20

pharmaceutically acceptable salts, thereof exhibits remarkable hair growth promoting activity which is superior in such regard to the corresponding (S)-enantiomer and the racemic mixture of such enantiomers. In fact, it has been found that the (R)-enantiomer is surprisingly and unexpectedly

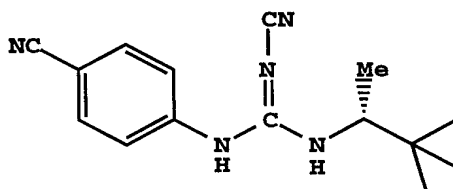
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more effective in stimulating hair follicles to produce hair growth at a substantially faster rate as compared to the corresponding (S)-enantiomer.

The above (R)-enantiomer of the invention has the structure I

30

I

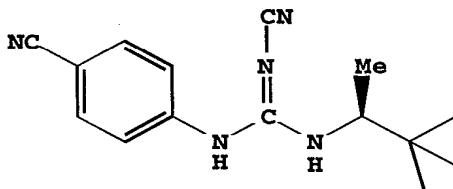


The (R)-enantiomer I will be in substantially pure form, that is, will be at least 99% pure (R)-enantiomer and will at most contain 1% (S)-enantiomer.

5 In addition, in accordance with the present invention, it has been found that the (S)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile, including pharmaceutically acceptable salts thereof, exhibits
10 excellent hair growth promoting activity.

The above (S)-enantiomer of the invention has the structure II

II



15 The (S)-enantiomer II will be in substantially pure form, that is, will be at least 99% pure (S)-enantiomer and will at most contain 1% (R)-enantiomer.

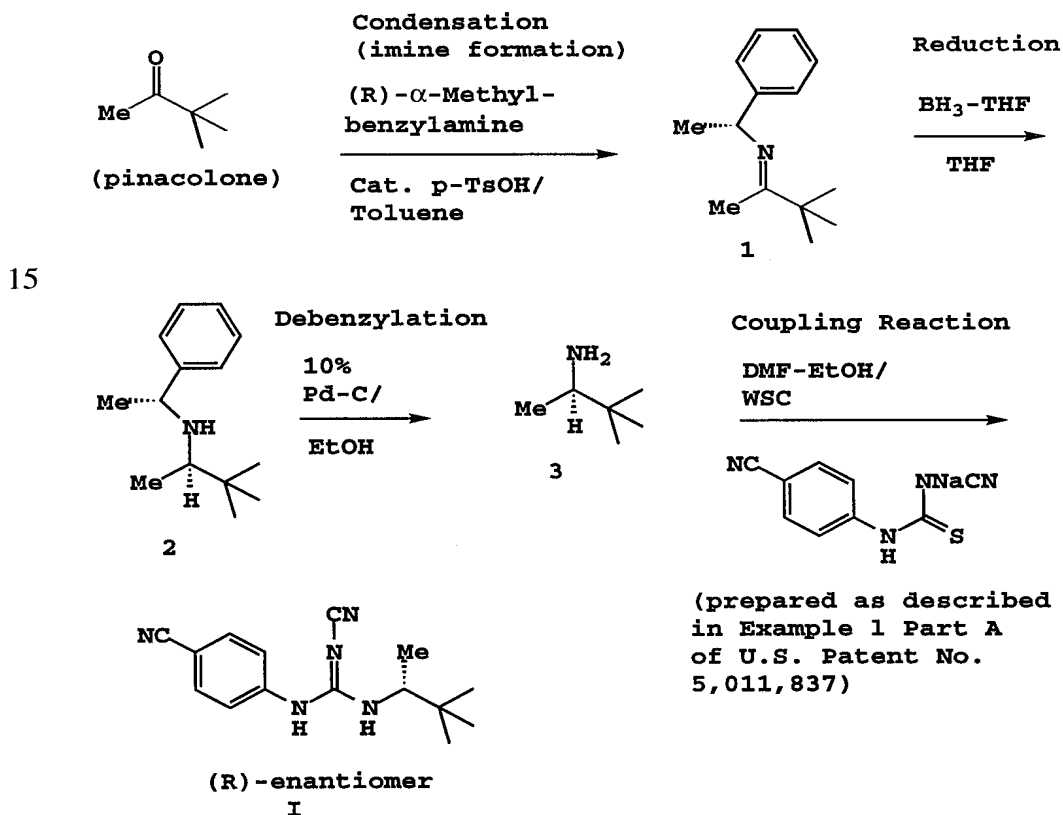
The enantiomers of the invention form salts
20 with a variety of inorganic and organic acids. The non-toxic pharmaceutically acceptable salts are preferred, although other salts may also be useful in isolating or purifying the product. Such pharmaceutically acceptable salts include those
25 formed with hydrochloric acid, methanesulfonic acid, sulfuric acid, acetic acid, maleic acid, and the like. The salts are obtained by reacting the product with an equivalent amount of the acid in a medium in which the salt precipitates.

30 The present invention also includes pharmaceutical compositions containing the (R)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile or a

pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

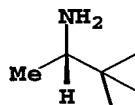
In addition, the present invention also includes pharmaceutical compositions containing the
 5 (S)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier therefor.

The (R)-enantiomer of the invention, that
 10 is, (R)-4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)-amino]methyl]amino]benzonitrile may be prepared according to the following reaction sequence:



The (S)-enantiomer of the invention, that is
 (S)-4-[[[(cyanoimino)[(1,2,2-trimethylpropyl)-
 amino]methyl]amino]benzonitrile may be prepared
 20 according to the above reaction sequence for
 preparation of the (R)-enantiomer except that (S)-

α -methylbenzylamine is employed in place of (R)- α -methylbenzylamine to eventually form



- 5 which is reacted with the 4-cyano-N'-(4-cyanophenyl)thiourea, monosodium salt to form the (S)-enantiomer (II).

The (R)-enantiomer I of the invention or the
10 (S)-enantiomer II of the invention may be formulation with other hair growth promoting compounds such as the potassium channel openers minoxidil (Upjohn) and/or diazoxide (Shiseido and Schering-Plough), as well as cromakalim and
15 pinacidil; a 5- α -reductase inhibitor such as finasteride (Merck's Proscar®), terazosin HCl (Abbott's Hytrin®), or doxazosin mesylate (Pfizer's Cardura®); and/or an androgen blocker such as 4-(5-methoxyheptyl)-hexahydro-2(1H)-pentalenone as
20 disclosed in PCT Application WO 92/09259A, vasoconstrictors such as betamethasone dipropionate, corticosteroids such as hydrocortisone, and scopolamine, and cyproterone acetate.

25 The enantiomers of the invention may be administered via topical, oral, parenteral or rectal routes as described in U.S. Patent No. 5,011,837 (incorporated herein by reference), with topical being preferred. Thus, the enantiomers of
30 the invention in suitable topical formulations are applied to the skin region where hair growth is desired.

Typical topical formulations for use herein will include conventional ointments, creams,
35 lotions, waxes, gels, pastes, jellies, sprays, aerosols and the like in aqueous or non-aqueous

formulations. Examples of suitable topical formulations are disclosed in U.S. Patent Nos. 4,139,619 and 4,596,812 which are incorporated herein by reference.

- 5 The enantiomers of the invention will be used in an effective amount, that is, in an amount sufficient to promote hair growth or treat hair growth disorders, such that hair growth is increased or produced. A typical topical
10 composition will include from about 0.01 to about 15% by weight, preferably from about 0.1 to about 10% by weight of the composition.

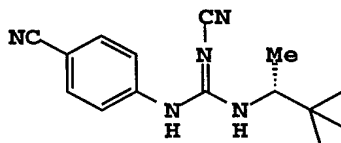
 The topical formulations containing the enantiomers of the invention can be applied to the
15 area to be treated such as the scalp in humans, by spraying, dabbing or swabbing to deliver the enantiomer to the region of the hair follicle. The formulations will be applied to the area of treatment on a routine basis prior to, during and
20 subsequent to hair growth, at least once daily, and preferably two or more times daily.

 The accompanying Figure is a graph showing the effect of a once daily application of each of the (R)- and (S)- enantiomers described herein on
25 hair growth in male C3H mice.

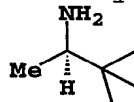
 The following Examples represent preferred embodiments of the present invention.

Example 1

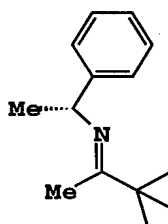
- 30 (R)-4-[[(Cyanoimino) [(1,2,2-trimethylpropyl)amino]-methyl]amino]benzonitrile



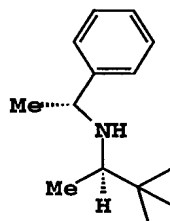
A. (R)-1,2,2-Trimethylpropyl amine



The title compound was prepared according to
5 the procedure described by Manley and Quast (*J.*
Med. Chem. **1992**, 35, 2327-2340) with some
modification. A mixture of pinacolone (29 g, 290
mmol), (R)- α -methylbenzyl amine (17.6 g, 145 mmol)
and p-toluenesulfonic acid monohydrate (300 mg) in
10 toluene (150 mL) was refluxed using a Dean-Stark
trap (to remove water from the reaction mixture)
for 3 days. The solvent was evaporated and the
residue was distilled at ca. 120-2°C (9 mm) to give
21 g (71% yield) of

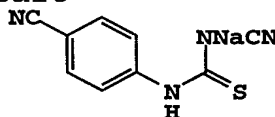


15 as a colorless oil. This material was dissolved in
anhydrous THF (210 mL) and treated at 0-2°C with
borane-THF complex (1M, 206 mL, 206 mmol). The
mixture was allowed to come to room temperature,
20 stirred for 5h and concentrated in vacuo. To the
resulting oily residue was carefully added ethanol
(300 mL), and the mixture was refluxed for 1h and
concentrated again in vacuo. The residue was
chromatographed over basic alumina (activity grade
25 1/hexane) giving colorless oil. Proton NMR and
HPLC (YMC C18 S3 4.6X50 mm column/water-MeOH-H₃PO₄
90:10:0.2 to 10:90:0.2 gradient) indicated that
this material was contaminated with ca. 10% of the
(S,R)-diastereomer. Therefore, this mixture was
30 resubjected to flash chromatography (silica
gel/hexane-EtoAc-triethylamine 95:5:0.1) to afford



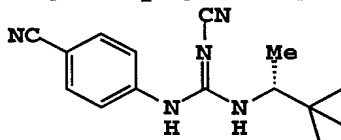
(11.45 g, 55.8 mmol, 54% yield). The above compound (11.45 g) and 10% palladium on carbon (1.5 g) were taken in EtOH (230 mL) and stirred under hydrogen for 12 hours. The mixture was filtered and the filtrate (ca. 230 mL) containing the title product was used as such for the next step as a ca. 0.24 M solution in ethanol (assumed 100% yield).

- 10 B. N-Cyano-N'-(4-cyanophenyl)thiourea, monosodium salt



The title compound was prepared according to Example 1 Part A of U.S. Patent No. 5,011,837.

- C. (R)-4-[[[(Cyanoimino)[(1,2,2-trimethylpropyl)amino]methyl]amino]benzonitrile

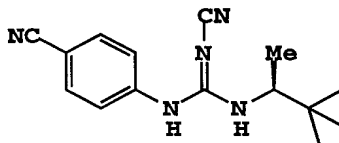


20 To a solution of Part B compound (6.0 g, 26.8 mmol) in DMF (150 mL) was sequentially added the solution of Part A compound (ca. 0.24 M in EtOH, 112 mL, 26.8 mmol) and 1-(3-dimethylamino-25 propyl)-3-ethylcarbodiimide hydrochloride (WSC) (6.0 g, 31.3 mmol). The mixture was stirred at room temperature for 3 hours, diluted with ethyl acetate and sequentially washed with 1N HCl, water and brine. The organic layer was dried over

- magnesium sulfate, concentrated and the crude product was purified by flash chromatography on silica gel (hexanes-ethyl acetate-triethylamine 75:25:0.2) to afford a colorless foam. This material was recrystallized from isopropanol to give the title compound as a white solid (4.15 g, 57.6%), mp 159-60°C; $[\alpha]_D^{-180^\circ}$ C=1, MeOH; enantiomeric purity determined by chiral HPLC = 99% (ChiralPak AD column/hexane-isopropanol-triethylamine 80:20:0.2); MS: 270 (M+H)⁺; ¹H NMR (CDCl₃) δ 8.65 (br s, 1H), 7.69 (d, 2H, J=8.79 Hz), 7.37 (d, 2H, J=8.79 Hz), 4.93 (br d, 1H), 3.83 (m, 1H), 1.10 (d, 1H, J=6.45 Hz), 0.90 (s, 9H).
- Elemental analysis: calculated for C₁₅H₁₉N₅:
C, 66.89; H, 7.11; N, 26.00
Found: C, 66.71; H, 7.14; N, 25.98.

Example 2

- (S)-4-[[[(Cyanoimino)[(1,2,2-trimethylpropyl)amino]-methyl]amino]benzonitrile



- The title compound was prepared from Part B compound of Example 1 and (S)-1,2,2-trimethylpropyl amine (prepared according to Manley and Quast, *J. Med. Chem.*, **1992**, 35, 2327-2340) by the same procedure as described in Example 1, Part C. The product was obtained as a colorless solid, mp 158-59°C; $[\alpha]_D^{+189^\circ}$ C=1, MeOH; enantiomeric purity determined by chiral HPLC = 99.4% (ChiralPak AD column/hexane-isopropanol-triethylamine 80:20:0.2); MS: 270 (M+H)⁺; ¹H NMR (CDCl₃) δ 8.43 (br s, 1H), 7.69 (d, 2H, J=8.79 Hz), 7.37 (d, 2H, J=8.79 Hz),

4.93 (br d, 1H), 3.83 (m, 1H), 1.10 (d, 1H, J=6.45 Hz), 0.90 (s, 9H).

Example 3

5 Comparison of Example 1-(R)-Enantiomer and Example 2-(S)-Enantiomer Re Hair Growth in an Animal Model

 The objective of the following described experiment was to compare and evaluate the in vivo
10 effect of the Example 1-(R)-enantiomer and the Example 2-(S)-enantiomer on hair growth in an animal model. The two enantiomers were compared topically for hair growth in C3H mice.

15 Animal Model

 The C3H mouse is a useful model for studying hair growth. Its usefulness rests with the fact that skin pigmentation of this animal is provided by the melanocytes of the hair follicle and not the
20 epidermis. In the telogen or the resting phase of the hair follicle, the skin is pink. In the earliest phase of anagen or the growth phase, there is sudden graying of the skin and as the anagen phase progresses the skin becomes darker in color.
25 In this study, visual observation was used as an in vivo assay of anagen induction. Furthermore as anagen develops, the skin thickness increases from a thin telogen skin to a measurably thickened anagen skin. Thus, recording the skin color and
30 microscopic thickness of skin from these mice offers a sensitive, quantifiable and convenient method of assessing the phases of hair growth.

 Groups of 20, six to seven week old male C3H mice with hair follicles in the resting phase of
35 hair growth were used. At this stage in their life, the hair follicles remain in the telogen phase for up to 30 days or longer. This provides

an adequate window of time to screen drugs. Compounds that improve hair growth stimulate the hair follicles from the telogen to the anagen phase. This stimulation is manifested by the shortening of the telogen phase of the hair follicle cycle.

Animals were anesthetized with ketamine/ rompun (100 mg/Kg and 12 mg/Kg) IP and the hair over a defined dorsal area were closely clipped.

Animals with pink skin were treated topically 1x daily, 5 days per week with 50 microliters of a 2% solution of Example 1-(R)-enantiomer and a 2% solution of Example 1-(S)-enantiomer or vehicle by itself, applied to the dorsal area. The vehicle employed was ethanol/propylene glycol/water, 60/30/10. Treatment was continued for at least 4-5 weeks.

Animals were observed daily for side effects and changes to the test sites. All observations were documented. Test sites were graded weekly for changes in skin color and hair growth. In this study drug effects were evaluated using the visual observation of skin changing from pink to gray and resulting in hair growth.

Results

The percent of animals that induced hair follicle stimulation during the treatment period is illustrated in the accompanying Figure below. The most significant observation made between the two enantiomers is the difference in the time of onset of follicle stimulation. The time of onset for the Example 1-(R)-enantiomer was day 7 compared to day 11 for Example 2-(S)-enantiomer. The time of onset for the vehicle control was day 28. By day 11 of treatment the Example 1-(R)-enantiomer caused hair follicle stimulation in 40% of the test mice

compared to only 5% with Example 2-(S)-enantiomer. By day 14, 50% of the animals treated with Example 1-(R)-enantiomer showed hair follicle stimulation compared to 25% for Example 2-(S)-enantiomer. By
5 day 28, 85% of the animals treated with the Example 1-(R)-enantiomer showed hair follicle stimulation as compared to 65% treated with Example 2-(S)-enantiomer. Thus throughout the treatment period, the group treated with Example 1-(R)-enantiomer
10 showed a higher incidence of hair follicle stimulation as compared to the group treated with Example 2-(S)-enantiomer.

The attached Figure shows the effect of 1x daily topical application of Example 1-(R)-
15 enantiomer and Example 2-(S)-enantiomer.

In conclusion, these results in the C3H mice indicate that there is a remarkable difference between the Example 1-(R)-enantiomer and the Example 2-(S)enantiomer in their effect on hair
20 follicle stimulation; in particular the (R)-enantiomer has a faster onset of action compared to the corresponding (S)-enantiomer.

These results are indeed surprising and unexpected especially in view of the vasorelaxant
25 potencies of each of these enantiomers, which is generally recognized as an indication of hair growth promoting properties (Side Effects of Vasodilator Therapy, W.A. Pettinger et al, Hypertension, 1988, Vol. 11, II-34 to II-36, and
30 Minoxidil Stimulates Cutaneous Blood Flow in Human Balding Scalps: Pharmacodynamics measured by laser Doppler velocimetry and photopulse plethysmography. R.C. Wester et al, J. Invest. Dermatol., 184, Vol. 82, 515-517).

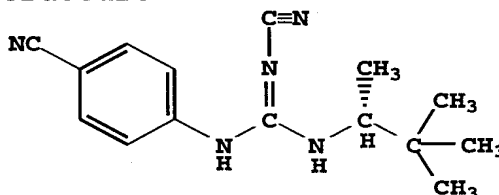
Thus, while the IC_{50} for vasorelaxant
potency of the (R)-enantiomer is 47 ± 17 nM versus
 157 ± 35 nM for the (S)-enantiomer, as seen above,
the hair growth promoting ability of the (R)-
5 enantiomer for producing hair growth within 11 days
of treatment is 8 times greater than the
corresponding (S)-enantiomer.

What is Claimed is:

1. The (R)-enantiomer of 4-[[[(cyanoimino)-
[(1,2,2-trimethylpropyl)amino]methyl]amino]-
benzonitrile or a pharmaceutically acceptable salt
5 thereof.

2. The (R)-enantiomer as defined in Claim 1
substantially separated from its corresponding S-
enantiomer.

3. The (R)-enantiomer as defined in Claim 1
10 having the structure



in substantially pure form.

4. The (R)-enantiomer as defined in Claim 1
having an enantiomeric purity equal to at least
15 99%.

5. A pharmaceutical composition comprising
the (R)-enantiomer as defined in Claim 1 and a
pharmaceutically acceptable carrier therefor.

6. A pharmaceutical combination which
20 comprises the R-enantiomer as defined in Claim 1 in
combination with another hair growth promoting
agent.

7. A method for promoting hair growth which
comprises administering to a human in need of
25 treatment a therapeutically effective amount of the
(R)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-
trimethylpropyl)amino]methyl]amino]benzonitrile or
a pharmaceutically acceptable salt thereof.

8. The method as defined in Claim 7 wherein
30 the (R)-enantiomer is administered systemically or
topically.

9. The method as defined in Claim 7 wherein
the (R)-enantiomer is administered topically.

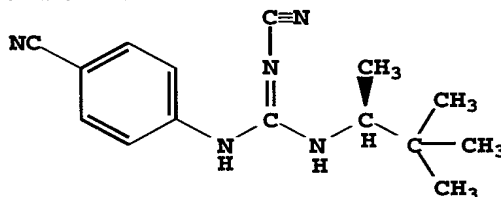
10. The method as defined in Claim 7 wherein the (R)-enantiomer is administered as a cream formulation, lotion formulation, liquid formulation or ointment formulation.

5 11. A method for treating male pattern baldness which comprises administering to a human in need of treatment a therapeutically effective amount of the R-enantiomer as defined in Claim 1.

12. The (S)-enantiomer of 4-[[[(cyanoimino)-
10 [(1,2,2-trimethylpropyl)amino]methyl]amino]-benzonitrile or a pharmaceutically acceptable salt thereof.

13. The (S)-enantiomer as defined in Claim 12 substantially separated from its corresponding
15 (R)-enantiomer.

14. The (S)-enantiomer as defined in Claim 12 having the structure



in substantially pure form.

20 15. The (S)-enantiomer as defined in Claim 12 having an enantiomeric purity equal to at least 99%.

16. A pharmaceutical composition comprising the (S)-enantiomer as defined in Claim 12 and a
25 pharmaceutically acceptable carrier therefor.

17. A pharmaceutical combination comprising the S-enantiomer as defined in Claim 12 in combination with another hair-growth promoting agent.

30 18. A method for promoting hair growth which comprises administering to a human in need of treatment a therapeutically effective amount of the (S)-enantiomer of 4-[[[(cyanoimino)[(1,2,2-

trimethylpropyl)amino]methyl]amino]benzonitrile or
a pharmaceutically acceptable salt thereof.

19. The method as defined in Claim 18
wherein the (S)-enantiomer is administered
5 systemically or topically.

20. The method as defined in Claim 18
wherein the (S)-enantiomer is administered
topically.

21. The method as defined in Claim 18
10 wherein the (S)-enantiomer is administered as a
cream formulation, lotion formulation, liquid
formulation or ointment formulation.

22. A method for treating male pattern
baldness which comprises administering to a human
15 in need of treatment a therapeutically effective
amount of the (S)-enantiomer as defined in Claim
12.

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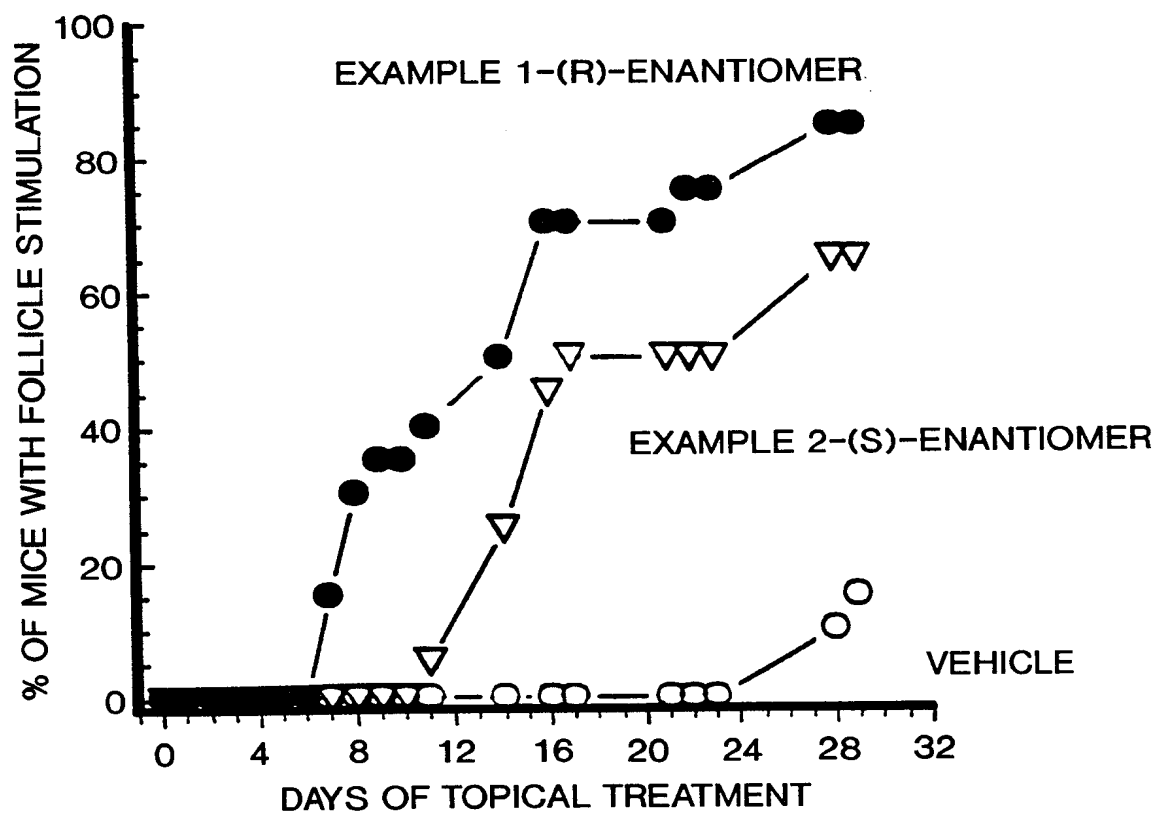
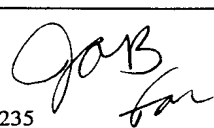


FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/16015

A. CLASSIFICATION OF SUBJECT MATTER IPC(6) : A61K 31/275; C07C 255/61 US CL : 514/524; 558/419 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/524; 558/419 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched None Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,011,837 A (ATWAL et al.) 30 April 1991, see entire document.	1-22
Y	US 5,578,599 A (DIANI et al.) 26 November 1996, see entire document.	1-22
Y	WO 92/09259 A1 (THE UPJOHN COMPANY) 11 June 1992, see entire document.	1-22
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means		
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 26 SEPTEMBER 1998	Date of mailing of the international search report 22 OCT 1998	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PETER G. O'SULLIVAN  Telephone No. (703) 308-1235	